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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/658,667	09/09/2003	Gary A. Koppel	22064-69748	3630

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EXAMINER	
RAE, CHARLESWORTH E	
ART UNIT	**PAPER NUMBER**
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/658,667	KOPPEL, GARY A	
	Examiner	Art Unit	
	Charlesworth Rae	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-32, 62-64, 92-103* is/are pending in the application.

4a) Of the above claim(s) *19,25,26,30-32,92-94 and 100* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,20-24,27-29,62-64,95-99,and 101-103* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/21/05;10/6/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response with traverse to the Restriction/Election requirements, mailed 11/29/06, electing invention II, and moxalactam as the beta-lactam species, humans as the warm blooded vertebrae species, Alzheimer's disease as the disease species is acknowledged and made of record. Applicant's statement that claims 62-64, 95-99, and 101-103 read on the elected species is acknowledged and made of record.

Applicant's statement canceling claims 78, 80-83, 90-91, adding new claims 92-103, and amending claim 63 and 64 is acknowledged and made of record. Applicant's statement that no new matter has been added by the amendment as new claims 92-103 ultimately depend from claim 62, and parallel those claims depending from claim 18 of invention 1, is acknowledged and made of record.

Status of the Claims

Claims 18-32, 62-64, and 92-103 are currently pending in this application and are the subject of the Office action.

Claims 19, 25-26, 30-32, 92-94, and 100 are withdrawn from examination for being directed to non-elected subject matter.

Claims 18, 20-24, 27-29, 62-64, 95-99, and 101-103 are presented for examination.

Restriction/Election

Applicant traverses the restriction requirement by admitting that invention I and invention II are not independent and distinct as the Examiner suggests. This admission is deemed to be persuasive. Thus, restriction between invention I and invention II is being withdrawn as inventions 1 & II are reasonably construed to be obvious variants for examination purposes.

Applicant's traversal argument that the election of species requirement regarding a warm-blooded vertebrae is improper because identical twins have different genetic characteristics is not deemed to be persuasive for the reasons previously made of record in the Office action mailed 11/29/06. Clearly, the cognitive ability of humans is reasonably considered to be distinctly superior to that of other warm-blooded vertebrae.

Applicant's traversal argument regarding election of species requirement regarding pharmaceutical formulations is deemed to be persuasive; this species requirement is withdrawn.

The restriction/election requirements are made final.

Claim rejections – 35 USC 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 USC 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 18, 20-24, and 27-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 recites the term *"said patient."* This term is indefinite as it lacks a proper antecedent basis. It is suggested that this term be deleted and replaced with the term "said vertebrae," provided this is supported by the specification as originally filed.

The dependent claims (20-24, and 27-29) are rejected for the same reason as independent claim 18 as these claims fail to correct the deficiency of the independent claim from which they depend.

Claim rejections – 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

LACK OF WRITTEN DESCRIPTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH:

Claims 18, 20-24, 27-29, 62-64, 95-99, and 101-103 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant invention is directed towards a method of enhancing cognitive function is a warm-blooded vertebrae (i.e.human) with Alzheimer's disease comprising administering an effective amount of compound capable of inhibiting the peptidase activity of one or more neurogenic peptidases in the brain of said vertebrae. The specification exemplifies moxalactam administered in effective amounts to inhibit NAALADase for evaluating its antiaggressive effects (page 67, line 15 to page 73, line

35). The specification, however, is deficient in that there is no information about which specific neurogenic peptidase or combination of peptidases that must be inhibited in order to enhance cognitive function (page 15, lines 3-30). The specification provides an extraordinarily long "laundry list" of a heterogeneously diverse group of disorders and effective amounts of peptidase inhibitor drugs (page 15, line 31 to 22, line 31). There is nothing to indicate that the amount of a peptidase inhibitor that is effective to inhibit NAALADase levels in the brain reasonably correlates with the improvement or enhancement of cognitive function either in the hamster or other warm-blooded vertebrae (see specification, page 5, lines 4-32; page 37, line 5 to page 39, line 6). The examples in the specification are not helpful for a few reasons (page 6, lines 14-23; page 40, line 15 to page 41, line 3; and page 49, line 29 to 93, line 5). First, the examples give no information as to how an effective amount of specific peptidase inhibitor would reasonably be effective in enhancing or improving cognitive deficits in other pathologically and/or clinical distinct conditions. Second, there is nothing to show that the exemplified peptidase inhibitors are representative of the entire genus as claimed. Third, the examples exemplify animal studies conducted in hamsters.

Thus, the specification does not provide the requisite written description to show that the applicant was in possession of the claimed subject matter.

Lack of Enablement under 35 USC 112, First Paragraph

Claims 18, 20-24, 27-29, 62-64, 95-99, and 101-103 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating

aggressive disorders (see Specification, page 10, lines 2-8), does not reasonably provide enablement for treating other conditions such as Alzheimer's .This is a scope enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if its is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth in *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman* 230 USPQ 546 (BdApls 1986) at 547 the court cited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art.

The instant invention is generally directed towards a method of enhancing/improving cognitive function in a warm-blooded vertebrae comprising administering an effective amount of compound capable of inhibiting the peptidase activity of one or more neurogenic peptidases in the brain of said vertebrae.

Instant specification disclose Behavioral studies with Moxalactam in animal Syrian golden hamsters in evaluating the effects of beta-lactams for treating offensive aggression (page 50, line 11 to page 75, line 27); Clauvulanic acid (CLAV) dose-response in the Seed Finding Model of anxiety and aggression in hamsters (specification, page 77, line 7 to page 92, line 26). Applicant's discloses that blocking NAALADase activity with beta-NAAG does not alter offensive aggression as tested in the resident-intruder paradigm (page 93, lines 1-3). Applicant also discloses that these findings are not inconsistent with the notion that clavulanic acid and beta-NAAG share a

common mechanism-blockade of NAALADase activity (page 93, lines 3-5). Applicant discloses that Moxalactam had no significant effect in binding assays testing for amino acids, adrenergic, serotoninergic, and dopaminergic receptors and their transporters, wherein thirty-six different assays by NOVASCREEN (page 72, line 1 to page 74, line 8). Applicant discloses that exemplary of cognitivie and behavioral disorders susceptible to treatment in accordance with the instant invention include aggressive disorder, obsessive compulsive disorder, anxiety, depression, ADHD, and memory impairment (page 3, lines 10-12). Applicant discloses that animal data suggest that the method and formulation of the instant invention have potential as an antiaggressive agent to control impulsivity and violence in autism, Tourette's syndrome, mental retardation, psychosis, mania, senile dementia and individuals with personality disorders and history of inappropriate aggression (page 3, lines 12-19). Applicant discloses that Moxalactam has been found to exhibit significant dose responsive neuroactivity when administered parenterally at least at about 50 μg/kg of body weight (page 4, line 26 to page 5, line 6). Applicant further discloses that in one embodiment of the invention the compound of the pharmaceutical formulation (for treatment with consequent reduction of symptoms of behavioral or cognitive disorders in patients in need thereof) is capable of binding to and inhibiting the function of a bacterial protease known to exhibit its proteolytic activity on a peptidoglycan substrate comprising the C-terminal peptide sequence acyl-D-alanyl-D-alanine; while in another embodiment the compound is capable of binding to beta-lactamase, another bacterial protein capable of binding to penicillin, and inhibiting the function of that enzyme (page 5, lines 7-18). Also,

applicant discloses that the amount of the inhibitor used in the formulation is that determined to be effective to inhibit the activity of endogenous NAALADase; the level of the activity exhibited by the NAALADase inhibitor is dependent on the affinity of the compound to bind penicillin-binding proteins and to NAALADase, as well as the ability of the inhibitor compound to cross the blood brain barrier to achieve levels in the brain effective to modify patient behavior and/or cognitive performance (page 5, line 18 to page 6, line 12). No dose response relationship is disclosed between the inhibitory compounds and improving/enhancing cognitive function in Alzheimer's disease (page 15, line 15 to page 22, line 31).

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. It is noted that the pharmaceutical art is generally unpredictable, requiring each embodiment to be individually assessed for physiological activity. The more unpredictable an area, the more specific enablement is necessary in order to satisfy the statue. (see *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970)). For example, the mode of action of central nervous system (CNS) acting drugs is often unknown or very unpredictable and administration of such agents is often accompanied by undersirable effects. Besides, there is a disproportionately sparse number of discovery of new and predictable curative treatments for neurodegenerative conditions as compared with the vast number of new drugs discovered.

Lockhart et al. teach that accumulating preclinical data now suggests that certain acethylcholinesterase, and M1 muscarinic receptor agonists are capable of stimulating App Amyloid precursor protein synthesis via the α-secretase pathway thereby avoiding

the allertante amyloidogenic β1-40/42 forming pathway (Lockhart et al. Cognition enhancing or neuroprotective compounds for the treatment of cognitive disorders: why? When? Which? Experimental Gerontology. 2003; 38(1-2):119-128, electronic copy, pages 1-17; see page 11, last paragraph). Lockhart et al teach that targeting the genesis of the various neurodegenerative disorders necessitates a therapeutic approach specific to each neurodegenerative disorder (page 11, second paragraph). Lockhart et al. disclose that by reducing the formation of plaque-promoting β1-40/42 peptides and promoting APP synthesis, cognitive enhancing compounds may have in addition to their symptomatic properties some disease-modifying actions , however, long-term clinical studies with AChEIs have not born out these interesting preclinical observations in terms of beneficial effects, and no significant reductions in the CSF levels of β1-40/42 has been observed in patients treated with cholinergic drugs (page 11, last paragraph).

Barco et al. teach that treatment of memory disorders, such as the gradual weakening of memory with age, the ravages of Alzheimer's disease and the cogniotive deficits in various forms of mental retardation, may greatly benefit from a better understanding of the molecular and cellular mechanisms of memory formation (Barco et al. CREB, memory enhancement and the treatment of memory disorders: promises, pitfalls and prospects. Expert Opin. Ther. Targets. 2003;7(1):101-114, abstract). Barco et al. disclose that substantial evidence in experimental systems ranging from mollusks to humans indicates that the cAMP response element binding protein (CREB) is a core componet of the molecular switch that converts short to long-term memory (abstract).

Barco et al. disclose it should be possible in principle to develop pharmaceuticals that enhance regulated CREB-mediated gene induction without excessively elevating uninduced, basal transcription of CREB-regulating genes, thereby possibly enhancing memory storage (page 110, last paragraph, lines 1-16). Barco et al. teach that the efforts at developing memomry-enhancing drugs might be more productively directed towards molecular targets with more specific expression and function than the CREB family of transcriptional regulators (page 110, last paragraph, last five lines).

Knopman teaches that cholinesterase inhibitor (CEI) drugs represent the only FDA-approved primary treatment options for AD (Knopman DS. Current pharmacotherapies for Alzheimer's disease. Geriatrics. 1998;53(Suppl. 1) S31-S34, **abstract only**).

2. The breadth of the claims

The instant claims are relatively broad in scope. For example claims 18 and 62 encompass a diverse group of numerous cognitive disorders, neurogenic peptidases, and neurogenic peptidase inhibitor drugs. Because the therapeutic response to be achieved would necessarily vary depending upon the specific pathological disorder, and the specific neurogenic peptidase that is inhibited by the neurogenic peptidase inhibitor, the level of predictably in practicing the claimed invention would be greatly diminished.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the the cognitive enhancing/improving effects of the exemplified neurogenic peptidase inhibitors (i.e. moxalactam and clavulanic acid) in treating neurodegenerative diseases. The 'working examples" are limited to evaluating the antiaggressive effects of the exemplified neurogenic peptidase inhibitors. Thus, the applicant at best has provided specific direction or guidance only for a general administration protocol for treating aggressive disorder. No reasonably specific guidance is provided concerning useful therapeutic protocols or specific agents for treating neurodegenerative diseases such as Alzhemier's disease.

4. The quantity of experimentation necessary

In view of the prior art, it is reasonable to surmise that the level of uncertainty in the art would require one skilled in the art to conduct more than routine experimentation in order to practice the claimed invention in humans with Alzheimer's disease. Thus, based on the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed methods could be predictably used as treatments for cognitive disorders in warm-blooded vertebrae.

For the reasons stated above, claims 18, 20-24, 27-29, 62-64, 95-99, and 101-103 are rejected under 35 USC 112, first paragraph, for lack of scope enablement because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claims.

Claim rejections – 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 18, 20-24, 27-29, 62-64, 95-99, and 101-103 are rejected under 35 USC 102(b) as being anticipated by Nichols et al. (Nicols et al. Coagulopathy associated with extended-spectrum cephalosporins in patients with serious infections. Antyimicrobial Agents and Chemotherapy. 1987;31(2): 281-285).

Nichols et al. teach moxalactam for treating patients with pneumonia or peritonitis (abstract). Moxalactam was was administered in doses of 2 to 4 g every 8 hours; dosage adjustments for renal impairment were made according to product labeling (page 281, second full paragraph). The mean age of the 34 evaluable patients who were treated with moxalactam was 61 (range 25-90); see Table 1, page 282. Patients who received moxalactam experienced a higher incidence of hypoprothrombinemia as compared to the other paitents who were treated with ceftizoxime and cefotaxime (abstract). To the extent that the instant method claims recite the step of administering moxalactam to a warm-blooded vertebrae as the only active step, coupled with the fact that patients about 50 years and older are reasonably construed to be suffer from Alzheimer's disease, albeit undiagnosed Alzheimer's disease, the contemplated cognitive enhancing/impoving effect to be achieved in practicing the instant claimed invention is deemed to be an inherent property of the known drug i.e. moxalactam. The

dose of moxalactam taught by Nichols et al. is construed to be *"an effective amount capable of inhibiting peptidase activity of one or more neurogenic peptidases in the brain of the a warm-blooded vertebrae in need of treatment."* The term *"at least 50 μg/kg but less than an amount effective to provide clinically effective antibacterial blood levels of the compound,"* as recited in claims 27 and101, is reasonably construed to mean any administered dose of moxalactam to a warm-blooded vertebrae in need thereof that leads to treatment failure. Nichols et al. abdominal distention was noted in 7 of 8 moxalactam patients who subsequently developed hypoprothrombinemia, which is reasonably construed to be evidence of moxalactam treatment failure (page 283, col. 2, first para. lines 3-6). The term *"wherein the β-lactam antibiotic is administered in an amount less than that necessary to obtain antibiotically effective blood levels of said antibiotic,"* as recited in claim 64, is reasonably construed to any administered dose of moxalactam to a warm-blooded vertebrae in need thereof that leads to treatment failure e.g. abdominal distension and hypoprothrombinemia. Thus, the instant claims 18, 20-24, 27-29, 62-64, 95-99, and 101-103 are anticipated by Nichols et al. for the above reasons.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http:pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 800-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

5 Jul 2007
CER

BRIAN-YONG S. KWON
PRIMARY EXAMINER